REMARKS

Claims 21, 24-40, 43, 50, 54-63, 69-80 , 101 and 102 are pending in this application.

Claim 21 is directed to plants that contain plant cells that express a non-plant biologically functional multimeric protein resulting from assembly of at least two different polypeptides. According to the method, the plant cells contain nucleic acid encoding the two different polypeptides each including a leader sequence which forms a secretion signal for individual polypeptide. As discovered by the inventors, proper processing of the each polypeptide is required so that the two polypeptides can form a biologically functional multimeric protein.

Claim 43 is directed to a plant cell containing nucleic sequence encoding an antigen-specific and containing the antigen specific immunoglobulin. In claim 43, the antigen-specific immunoglobulin is encoded by a heavy and light chain polypeptide.

Claim 21, 26 and 63 have been amended. The amendments have been made to clarify the invention that Applicants wish to pursue and raise no issue of new matter. Claim 63 has been amended to replace "derived" with "obtained." Applicants submit that the amendment of does not limit the claim scope and that the terms "derived" and "obtained" have similar meaning and scope in the context of the claim.

New claims 103-106 have been added. Thus, the new claims are fully supported by the application and raise no issue of new matter. Support for claim 102 is found in the application at page 12-14. Support in claim 103 for "two or four different polypeptides" is found in the application at page 10, lines 12-13 (definition of multimeric protein) and at page 35, lines 5-12 (discussing secretory IgA).

REQUEST TO CORRECT INVENTORSHIP

Applicants again reiterate their request for a decision on the earlier filed request to correct inventorship under 37 C.F.R. § 1.48(b). The Request was filed along with the Request for Continued Prosecution Examination (CPA) on February 28, 2002. A copy of

the CPA transmittal as filed requesting the inventorship change is attached herewith. An indication whether or not inventorship has been amended is earnestly solicited.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (Written Description)

The rejection of claims 21, 24-27, 29, 30, 39, 40, 78, 80 and 101 as being allegedly failing to comply with the written description requirement is respectfully submitted to be in error for the following reasons.

Applicable legal standard

The proper standard for determining compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, is whether the specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. *See* MPEP § 2163.02 (citing *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985)). The subject matter of the claimed invention need not be described literally in the specification in order to satisfy the requirements of 35 U.S.C. § 112, first paragraph. *Id.* In a careful analysis of the written description requirement provided by the Patent and Trademark Office in its *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶1, "Written Description" Requirement*, it is stated that an adequate written description "may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." 66 Fed. Reg. 1099, 1105 (2001) (emphasis added).

The specification provides adequate written description for claims **21, 24-27, 29, 30, 39, 40, 78, 80 and 101.**

The Examiner has rejected all claims that relate to plant cells with nucleic acid encoding biologically functional multimeric protein comprising at least two different polypeptides. Although the Examiner appears to admit that the specification provides

adequate written description for plant cells expressing antibodies, it is concluded that this does not constitute a substantial portion of the genus of cells expressing different multimeric proteins.

It is respectfully submitted that this conclusion is in error. First, Applicants point out that the inventors' original success with expressing the 6D4 IgG class catalytic antibody in plants led directly to the successful expression in plants of a complete IgA secretory immunoglobulin. Secretary IgA is a complex multisubunit protein, requiring the assembly of ten subunits representing four different polypeptides. Secretory IgA is a dimeric molecule, the monomers stabilized by a J chain and a secretory component.

Example 15 of the patent application at pages 90-102 describes the process used for expressing secretory IgA in plants . An IgA like heavy chain was formed from the $V_{H\gamma}$, $C_{H\gamma}1$ and $C_{H\gamma}2$ domains of the Guy 13 antibody heavy chain and $C\alpha2$ and $C\alpha3$ domains of the MOPC 315 IgA myeloma heavy chain. *Id.* at Page 91. A plant cell was then prepared containing nucleic acid encoding the hybrid heavy chain, the Guy 13 kappa light chain, a mouse J (Joining) chain (Page 96) and a mouse secretory component (page 96). Ten transgenic plants were produced in which all expressed a fully assembled secretory IgA molecule of 470Kd. *Id.* at page 98. Proper assembly of plant produced secretory IgA was demonstrated by the molecular weight and by binding activity curves which showed similar results to native antibody from hybridoma cells. *Id.* at page 99.

Notably, assembly of the multimeric secretory IgA was very efficient, involving more than half of the total antibody. *Id.* at page 100. Furthermore, this was achieved by using an identical expression system for each subunit; i.e., the same leader sequence and promoter (35S transcript of cauliflower mosaic virus) were used.

Thus, it is respectfully submitted that one skilled in the art would acknowledge that the application provides substantial evidence supporting the ability of plant cells to assemble complex multimeric proteins. In addition, nucleotide sequence encoding a wide array of multimeric proteins is readily available in public repositories and the skill in the art

of protein expression should be considered very high. Furthermore, the inventors have demonstrated highly successful assembly of two very different type of immunoglobulins, one a tetrameric (4) multichain immunoglobulin formed from two polypeptides and the other a decameric (10) multi-chain immunoglobulin formed from four different polypeptides. One skilled in the art would acknowledge that successful assembly of these two different immunoglobulins predicts success not only for immunoglobulins but also for other members of immunoglobulin gene superfamily, a large family of structurally related proteins (see application pages 12-13).

Furthermore, the evidence that the inventors possessed the claimed invention extends beyond the immunoglobulin gene superfamily to a significant and substantial portion of the claimed genus of multimeric proteins. The inventors' success in obtaining high efficiency assembly of a very complex multimeric protein such as secretory IgA, which requires assembly of both immunoglobulin gene superfamily polypeptides (heavy and light chains) and two different non-immunoglobulin gene superfamily polypeptides (J chain and secretory component) in plant cells, speaks loudly to possession of multi-chain assembly in plants that goes beyond the immunoglobulin gene superfamily of multimeric proteins. Furthermore, the highly successful expression in plants of immunoglobulins, which are very specialized proteins having no counterparts in plants, also renders likely the successful assembly in plants of non-plant proteins that are related to those in plants and even unrelated to those in plants. The inventors have clearly demonstrated direct applicability of genetic expression knowledge from animal cells including mammalian cells to plant cells.

It is respectfully demonstrated that the inventors were in possession of a broad genus based in part on very successful demonstrations of assembly with disparate and complex multimeric proteins from the immunoglobulin gene superfamily (and including assembly with some non-Ig gene superfamily polypeptides) and in part with the high level of skill in the art. Applicants are entitled to broad scope even though only a small portion of the claimed genus has been actually reduced to practice. See interim guideline written

description requirements, Federal Register vol. 66, no. 4, 1/5/01, II(A)(3)(a)(2). Applicants respectfully request the Examiner to reconsider and withdraw the rejection.

Although Applicants believe that claim 21 is supported by an adequate written description, Applicants wish to point out that new claims 103-106 differ in scope from claim 21 and, therefore, should be separately addressed.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (Enablement)

The rejection of claims 21, 24-40, 43, 50, 54-63, 69-80 and 101-102 because the specification allegedly fails to enable these claims respectfully submitted to be in error for the following reasons.

Applicable legal standard

It is well established in the patent law that a specification is presumed to be enabling. Also, as stated in MPEP § 2164.04, "it is incumbent on the Patent Office... to explain why it doubts any statement in a disclosure, and to back up its assertions of its own with acceptable evidence or reasoning.... Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." Moreover, a broad allegation by an examiner that a disclosure is speculative, coupled with various difficulties that might be encountered in practice, is not a sufficient basis for requiring proof of operability. *In re Chilowsky*, 229 F.2d 457, 463 (CCPA 1956) (*n.b.*, this case was recently cited by the Board for precisely this proposition in *Ex parte Miyada*, Appeal No. 1997-3535, page 5).

***The specification enables claims* 31-38 43, 50, 54-63, 69-77, 79, and 102.**

Applicants respectfully point out that this rejection has been improperly applied with respect to claims 31-38 43, 50, 54-63, 69-77, 79, and 102, all directed to cells expressing immunoglobulin. Specifically, the rejection lacks any rationale for why these claims would not be enabled. Furthermore, the Examiner clearly states at page 4 of the Office Action that the specification enables plant cells containing antigen-specific

antibodies. Accordingly, the Examiner is respectfully urged to withdraw the rejection of these claims for allegedly lacking enablement.

***The specification enables claims* 21, 24-27, 29, 30, 39, 40, 78, 80 and 101.**

The Examiner argues that it would require undue experimentation to assemble non-plant multimeric protein other than immunoglobulin because "expressing the different polypeptides in a manner that would allow for assembly in a plant cell is unpredictable, as numerous variables may affect assembly including but not limited to the level and location of expression as well as the presence of other cellular factors that may be required for multimer assembly." Paper no. 27, page 5.

Applicants respectfully disagree. The rejection applies a view of the field that existed prior to but not after the inventors' breakthrough discovery that plants could be used to express not only heteromultmeric non-plant protein but even very specialized such proteins that have no counterpart in plants. In particular, the inventors achieved assembly of heteromultimeric protein using methods that were in common at the time; No special methods were needed to achieve expression of secretory IgA, which is a very complex heteromultimeric protein comprising 10 subunits requiring expression of four different polypeptides. Furthermore, the J chain and secretory component members of the assembled IgA are not even immunoglobulin gene superfamily members. The evidence of record supports that Applicants' success enables expression of a wide variety of non-plant proteins in plants.

Although one needs to know which subunits make up the multimeric protein, this is something readily determined from the cells that naturally produce the multimeric protein. It also might be helpful to know the relative level of expression of each subunit polypeptide in its natural state as a starting point for expression. Differences in subunit expression levels in plant cells may readily be achieved, however, using promoters of differing strength as is well known in the art. However even this is not critical for the claimed invention as demonstrated the inventors successful assembly of secretory IgA. As already discussed, the four different polypeptides that make up this 10 subunit multimeric protein were all expressed using the same promoter and signal sequence.

Thus, the instant rejection is flawed because it is based on concerns about non-plant protein expression in plants that have been eliminated or reduced dramatically in significance following the work of the inventors.

Furthermore, the claims do not require 100% assembly of multimeric non-plant polypeptide subunits in plant cells or even assembly levels that are similar to those in cells that naturally produce the multimeric protein. Thus, the Examiner's rejection is also flawed for using a standard not commensurate with the claims.

The Examiner's attempts to support the rejection by citation to scientific articles describing heteromultimeric protein expression in cells that naturally express the protein. However, as addressed below, these references do not evidence non-enablement of the claimed invention.

According to the Examiner, Lippencott-Schwartz et al. supports lack of enablement because it teaches that the T cell receptor subunit proteins are expressed at different levels in T cells. However, nothing in Lippencott-Schwartz teaches that an alteration in the relative levels of expression of TCR subunits in a plant cell will not result in assembly of polypeptides into a functionally active T cell receptor. As already mentioned, the claims do not require 100% efficiency of assembly or even assembly levels that are similar to those in cells that naturally produce the multimeric protein. Furthermore, the Examiner has failed to consider that adjustments in subunit expression level are routinely achieved in the art using, for example, promoters of different strength, as is taught by the specification.

Also according to the Examiner, Waldman et al. supports lack of enablement because this reference teaches that while current is increased by co-expression of a sodium channel gamma subunit with a sodium channel alpha subunit as compared to expression of the alpha alone, the T cell receptor subunit proteins are expressed at different levels in T cells. However, nothing in Waldman et al. that would indicate that the delta chain would not associate with the beta and gamma sodium channel polypeptide chains in plant cells as it did in frog oocytes as demonstrated by Waldman et al. Quite to

the contrary, Applicants submit that Waldman et al. demonstrates predictability of expressing multimeric sodium channel subunits in non native cells.

Further according to the Examiner, Bonifacino et al. supports lack of enablement because this reference teaches that in the absence of expression of the delta subunit, other TCR subunits are synthesized at their normal rates but are retained in the endoplasmic reticulum where they are degraded, and that failure to produce sufficient alpha or beta subunit results in incomplete receptor and endoplasmic reticulum degradation. However, Bonifacino et al. teaches nothing more that the well known fact that a functional multimeric protein requires sufficient quantities of the subunits. A similar phenomena occurs in immune B lymphoid cells were heavy chain is retained in the endoplasmic reticulum and not secreted unless the cells also express the light chain. This allegedly significant variable was readily overcome by the inventors. Furthermore, the ordinarily skilled artisan wishing to practice the claimed methods need not understand the consequences of imbalanced expression levels and how subunits become degraded as a consequence. As already discussed, the invention does not require 100% assembly of the expressed non-plant protein and there is much knowledge in the art and teaching in the specification to adjust the levels of subunits as needed.

Lastly, according to the Examiner the publication by Yu et al. teaches that heme is required to assemble NAPDH oxidase cytochrome b558, a heteromultimeric protein comprising two different polypeptides. Although there may be some rare cases where host factors needed for assembly of non-plant multimeric proteins may be lacking in plants, it is respectfully submitted that this would be known or readily determined in each case. However, one of ordinary skill using the present specification and the knowledge in the art could readily modify plant cells to provide any missing host factor. In the case of heme, it is noted that plant cells have heme oxygenase but that this is associated with the cytoplasm in plant cells rather than membrane bound as in animal cells. See Muramoto et al., Plant Physiol. 130:1958-1966 (2002); attached as Exhibit A. It is respectfully submitted that it would not require undue experimentation to determine if plant heme oxygenase could be used to assemble NAPDH oxidase cytochrome b558 in plant cells nor

would experimentation be undue to co-express animal heme oxygenase in plants together with NAPDH oxidase cytochrome b558.

It is respectfully submitted that the number of variables of significance that need to be considered to perform the claimed methods is small. This taken together with the high level of skill in the art and the successful demonstrations of heteromultimeric non-plant protein expression described in the specification demonstrates clearly that the claimed subject matter is supported by an enabling disclosure. The Examiner has failed to set forth a *prima facie* rejection for lack of enablement and is respectfully urged to reconsider and withdraw the rejection of claims 31-38 43, 50, 54-63, 69-77, 79, and 102.

Although Applicants believe that claim 21 is supported by an enabling disclosure, Applicants wish to point out that new claims 103-106 differ in scope from claim 21 and, therefore, should be separately addressed.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The claims have been variously rejected under 35 U.S.C. §112, second paragraph. Reconsideration is respectfully requested in view of the amendments and remarks below.

Applicable Legal Standard

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed. Cir. 1994). Recognizing that the English language is not always precise, the settled law has established that the essential inquiry in a definiteness analysis is whether the claims set out and circumscribe the claimed subject matter with reasonable particularity. *See, e.g.,* MPEP § 2173.02; *see also, Miles Laboratories, Inc. v. Shandon, Inc.*, 27 USPQ2d 1123, 1127 (Fed. Cir. 1993) ("If the claims read in the light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.") (emphasis added).

Definiteness is not analyzed in a vacuum, but in light of the content of the specification, and with the knowledge available to the skilled artisan.

Claim 21 ("biologically functional")

The Examiner has deemed claim 21 to be indefinite for reciting "biologically functional" because it is allegedly unclear in what way the multimeric protein is "biologically functional." According to the Examiner, the identity of the multimeric protein is not recited in the claim and that any protein would "presume to have a biologic function." Paper no. 27, page 8.

The Examiner's rationale for the rejection does not indicate why this term would be unclear. One skilled in the art knows that all proteins have one or more biological functions, which is a biological activity that the protein performs when its expressed in its native state. The specification teaches the well known fact that biological activity of proteins, particularly, multimeric proteins depends on proper assembly of the subunits. Page 1, lines 21-28, page 15, lines 8-10. For example, the patent application describes as a biological function, ligand binding or in the case of an immunoglobulin, antigen binding, formation of a catalytic reaction product, the release or uptake of energy and the like. See Page 15, lines 10-33, and page 23, lines 16-24.

It would be impossible for Applicants to recite all possible biological activities for each and every non-plant multimeric protein falling under the claim. It is respectfully submitted that the claim is reasonably clear because one skilled in the art would understand that that phrase "biological function" is a reference to a biological function of the multimeric protein that is inherent in the protein when properly assembled. Such information is well known or could be easily determined. The breadth of the claims should not be equated with indefiniteness. See *In re Miller*, 441 F.2d 689, 269 USPQ 597 (CCPA 1971).

Claim 21("at least two different polypeptides")

The Examiner has deemed Claim 21 to be indefinite for reciting "at least two different polypeptides" allegedly because the number of different polypeptides that the multimeric protein may comprise is unclear and that the claim sets no upper limit. It is unclear to Applicants how there can be any ambiguity in the phrase "at least two different polypeptides," which can only mean two or more. The Examiner's concern that Applicants set some upper limit does not appear to be an appropriate basis for a rejection under §112, second paragraph.

Furthermore, Applicants respectfully submit that there is no need to specify a particular upper number limit for the claim because it is well known in the art that the number of different subunits that assemble to form each particular multimeric protein is a characteristic of each protein and is well known or readily determinable. For example, IgG class immunoglobulin multimeric proteins comprises two different polypeptide while secretory IgA class immunoglobulin multimeric proteins comprises four different polypeptides. Again, the Examiner appears to be confusing the breadth of the claims with indefiniteness. See *In re Miller*, 441 F.2d 689, 269 USPQ 597 (CCPA 1971).

Claim 21("not normally produced by plants")

Claim 21 has been deemed to be indefinite for reciting "not normally produced by plants" allegedly because this phrase might cover native plant genes that only expressed under unusual conditions. Applicants have amended claim 21 to recite "not naturally produced by plants." It is respectfully submitted that this amendment eliminates the claim from reading on genes that reside naturally in plants or are expressed in plants do to infection that occurs in nature.

Claim 26 ("forms a binding site")

Claim 26 and dependent claims have been deemed to be indefinite for reciting that a multimeric protein forms a "binding site." The Examiner wonders whether this is the same as having a binding site. Applicants submit that this phrase is clear because in the context of multimeric protein assembly, the protein "forms" a binding site upon proper assembly. The protein once properly formed would comprise the binding site. Applicants have amended the claim make this more explicit.

Claim 63 ("derived")

The rejection of Claim 63 under 35 U.S.C. § 112, second paragraph as being indefinite because of the word "derived" is respectfully traversed. The Examiner alleges that "derived" does not indicate what would be retained by the algal plant from which the plant cell is derived. It is respectfully submitted that this constitutes circular reasoning and does not state any basis to support why derived is indefinite. Nevertheless, Applicants have amended the claim to recite that the plant cell is obtained from the algal plant. It is Applicants' position that both terms mean the same in this context.

REJECTION FOR DOUBLE PATENTING

Claims 21, 24-40, 43, 50, 54-63, 69,-80 and 101-102 have been rejected for obviousness-type double patenting as being unpatentable over claims 1-69 of U.S. Patent No. 6,417,429. Attached herewith is a terminal disclaimer linking the instant application to the term of U.S. Patent No. 6,417,429. Accordingly, the rejection has been obviated and should be withdrawn.

Atty. Dkt. No. EPI3007D
(formerly TSRI 184.2C3)

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is urged to contact the undersigned by telephone to address any outstanding issues standing in the way of an allowance.

Respectfully submitted,

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